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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/077,615	10/23/98	ARGUELLO	R 740380CSA

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EXAMINER	
EINSMANN, J	
ART UNIT	**PAPER NUMBER**
1655	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/077,615	Applicant(s) ARGUELLO ET AL.	
	Examiner Juliet C Einsmann	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-76* is/are pending in the application.

4a) Of the above claim(s) *70-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-69, 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *23* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 7/24/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/077615 is acceptable and a CPA has been established. An action on the CPA follows.

2. This action is written in response applicant's correspondence submitted 7/24/01, paper number 22. All previously pending claims were cancelled, and claims 55-76 were added. Claims 59-76 are pending and are subject to restriction as indicated below. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 55-69 and 73-76, drawn to methods for identifying nucleic acid molecules, classified in class 435, subclass 6.

II. Claims 70-71, drawn to kits, classified in class 536, subclass 23.1.

III. Claim 72, drawn to a computer system, classified in class 702, subclass 19.

The inventions are distinct, each from the other because of the following reasons:

4. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product

as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the products of group II can be used in other methods, such as for running samples on gels, nucleic acid purification methods, and methods for analyzing nucleic acid sequence diversity.

5. Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the computer of claim 72 can be used for a myriad of other methods, such as for word processing and for nucleic acid sequence analysis.

6. Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions the kits of invention II are drawn to products with completely different structural and functional properties.

7. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-III require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

8. During a telephone conversation with Mark Kassel on 9/19/01 a provisional election was made without traverse to prosecute the invention of group I, claims 55-69 and 73-76.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 70-72 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

9. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

10. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). The CRF submitted with the response to the Office Action had errors which prevented it from being entered into the database (see CRF Problem Report mailed with the previous action (paper number 19)). Further, there are sequences in the specification which are not identified with a proper sequence identifier (see, for example, p. 35). Applicant is required to submit a new CRF, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

11. A substitute specification excluding the claims is required pursuant to 37 CFR 1.125(a) for the following reasons

(A) Most of the pages of the specification do not have proper margins at the bottom of the page, and a number of these even have text that is cut off (for example, pages 1, 41, and 42). Applicant is reminded that MPEP 601 requires

> "Each sheet must include a top margin of at least 2.0 cm. (3/4 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 2.0 cm. (3/4 inch) and a bottom margin of at least 2.0 cm. (3/4 inch), and no holes should be made in the sheets as submitted. The lines of the specification, and any amendments to the specification, must be 1 ½ or double spaced. The pages of the specification including claims and abstract must be numbered consecutively, starting with 1, the numbers should be centrally located above or, preferably, below the text. See 37 CFR 1.52(b) and MPEP § 608.01."

(B) Page 43 of the specification is missing.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

Claim Objections

12. Claim 73 is objected to because the method step which follows step (e) and precedes step (g) is marked using an (1). This step should be labeled using an (f).

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 55-69 and 73-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "exact migration value" in claims 55-69 and 73-76 appears to represent new matter. Furthermore, the new limitations in claims 65 and 76 appears to represent new matter. Applicant identified locations in the specification which provide basis for the new claims, however, a careful review of these sections did not provide basis or definition for an "exact migration value." Furthermore, the two step process provided in claim 76 does not appear to be provided for in the specification. Applicant did not provide a page number for the basis for the limitation in claim 65, and a review of the specification did not locate a basis.

15. Claims 55-69 and 73-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 55-59 and 73-76 are indefinite over the recitation of "exact migration value" because the metes and bounds of this limitation are unclear. The specification does not provide a definition for this phrase, and therefore, it is not clear how this phrase limits the claims. For example, it is not clear if an "exact migration value" can be considered the consistent location of

a specific duplex on the gel, thus a visual assessment and comparison of the duplex in the gel represents the assignment of an exact migration value, or if an "exact migration value" requires that some numeric value be associated with the migration of a duplex.

Claim 59 is indefinite because it recites a list of arbitrary abbreviations representing gene names which are not defined in the claim or the specification. Thus, it is unclear what the genes being described actually are.

Claims 61 is indefinite over the recitation of "mammalian HLA alleles and human HLA alleles" because the claim is confusing. This is confusing because HLA stands for **human** lymphocyte antigen alleles. Thus, it is not clear what "mammalian HLA alleles" actually encompasses if not human HLA alleles.

Claim 73 is indefinite because the phrase "the single stranded DNA" lacks proper antecedent basis in the claim. The claim previously recites a "double stranded DNA" and a "stranded DNA" but not a single stranded DNA.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 55-67, 69, and 73-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimmerman *et al.* (Nucleic Acids Research, 1993, Vol. 21, No. 19, 4541-4547).

Zimmerman *et al.* teach a method for identifying an HLA gene comprising:

(a) hybridizing a single strand DNA molecule with a complementary labeled reference DNA strand to form a test duplex (p. 4542, heading "DHDA");

(b) separating the test duplex from at least one control duplex (p. 4542, heading "DHDA"); and

(c) detecting the positions to which the test duplex and the at least one control duplex migrate in the separation (p. 4543 and Fig. 2 and Fig. 3).

(d) assigning an exact migration value to the position to which the test duplex migrates (see figure 3);

(e) identifying the DNA molecule by matching the exact migration value with a database of migration values of identified DNA molecules (figures 2 and 3).

(f) repeating steps (a)-(e) one or more times wherein a different allelic strand is used in each repeat to identify the DNA molecule (see figure description for figure 3, the test was run with both DQA1*0102 and DQA1*0501 as the reference probe).

Zimmerman *et al.* use sequence specific oligonucleotide analysis to confirm the identity of the alleles tested (see Figure 3 legend). The method taught by Zimmerman *et al.* can distinguish the second exons of alleles 0102 and 0103, and these differ by only two nucleotides (see figures 1 and 2). In the methods taught by Zimmerman *et al.* the complementary reference strand and the DNA molecule have the same number of nucleotides, as these are both fragments amplified using the same primers (p. 4542). In the method taught by Zimmerman *et al.* the control duplexes are duplexes which have graded motilities and which are run in a different lane on the gel to the test duplex. Zimmerman *et al.* specifically teach that "every DQA1 allele, with the exception of DQA1*0601 can be distinguished by the unique mobility of one or both of its

HD bands." Zimmerman *et al.* teach steps prior to step (a) which include amplifying a DNA molecule to produce double stranded DNA molecules and denaturing the amplified double stranded DNA molecules into single use PCR prior to step (a) (see p. 4542, PCR amplification) and then denature the amplified double stranded DNA molecule into single stranded DNA molecules (see p. 4542, DHDA).

This rejection applies to these claims wherein assigning an exact migration value is interpreted to mean the consistent location of a specific duplex on the gel, thus a visual assessment and comparison of the duplex in the gel represents the assignment of an exact migration value. Zimmerman *et al.* demonstrate the use of their method for the determination of HLA DQA1 type for a family. In order to do so, they run the heteroduplexes out on an electrophoretic gel, assess the position of the bands, compare the test duplexes to a database of reference duplexes. The left side of the gel in Figure 3 is considered to be a database of test duplex migration values. With regard to claim 76, the assignment of migration values which are comparative to the control duplex is inherent in the method taught by Zimmerman *et al.* because the determination of the alleles present is a matter of comparison between the database of reference duplexes and the test duplexes. Thus, the determination of the allele present is a matter of comparing the distance traveled between the reference duplexes and the test duplexes.

Claim Rejections - 35 USC § 103

18. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* Zimmerman *et al.* teach a method for identifying an HLA gene comprising:

(a) hybridizing a single strand DNA molecule with a complementary labeled reference DNA strand to form a test duplex (p. 4542, heading "DHDA");

(b) separating the test duplex from at least one control duplex (p. 4542, heading "DHDA"); and

(c) detecting the positions to which the test duplex and the at least one control duplex migrate in the separation (p. 4543 and Fig. 2 and Fig. 3).

(d) assigning an exact migration value to the position to which the test duplex migrates (see figure 3);

(e) identifying the DNA molecule by matching the exact migration value with a database of migration values of identified DNA molecules (figures 2 and 3).

(f) repeating steps (a)-(e) one or more times wherein a different allelic strand is used in each repeat to identify the DNA molecule (see figure description for figure 3, the test was run with both DQA1*0102 and DQA1*0501 as the reference probe).

This rejection applies to these claims wherein assigning an exact migration value is interpreted to mean the consistent location of a specific duplex on the gel, thus a visual assessment and comparison of the duplex in the gel represents the assignment of an exact migration value. Zimmerman *et al.* demonstrate the use of their method for the determination of HLA DQA1 type for a family. In order to do so, they run the heteroduplexes out on an electrophoretic gel, assess the position of the bands, compare the test duplexes to a database of reference duplexes. The left side of the gel in Figure 3 is considered to be a database of test duplex migration values.

Zimmerman *et al.* do not teach a method in which the identified DNA molecule is matched to a second identified DNA molecule and the method is used to match tissue between a prospective tissue donor and prospective tissue recipient. However, Zimmerman *et al.* do teach that identifying the molecular diversity within MHC class II molecules has been motivated in large part by the clinical significance of matching donor and host in solid organ and kidney transplants (p. 4541), and that their method provides many advantages over the state of the art SSO-typing methodologies, including a reduced number of probes needed and the ability to use lower stringency conditions, thus eliminating the need for tight control of hybridization and washing conditions, since identification is based o n the detection of HD products with unique electrophoretic mobilities (p. 4545). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the method of genotyping taught by Zimmerman *et al.* for tissue donor matching since Zimmerman *et al.* teach the need for typing methods in donor-tissue situations, and Zimmerman *et al.* provide a method with the benefits as discussed.

19. Claims 55-69 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* in view of Mullins *et al.* (WO 95/01453).

This rejection applies to the claims when "exact migration value" is interpreted to require the assignment of a numerical value to the distance traveled by the heteroduplexes.

Zimmerman *et al.* teach a method for identifying an HLA gene comprising:

(a) hybridizing a single strand DNA molecule with a complementary labeled reference DNA strand to form a test duplex (p. 4542, heading "DHDA");

(b) separating the test duplex from at least one control duplex (p. 4542, heading "DHDA"); and

(c) detecting the positions to which the test duplex and the at least one control duplex migrate in the separation (p. 4543 and Fig. 2 and Fig. 3).

(d) assigning a migration value to the position to which the test duplex migrates (see figure 3);

(e) identifying the DNA molecule by matching the migration value with a database of migration values of identified DNA molecules (figures 2 and 3).

(f) repeating steps (a)-(e) one or more times wherein a different allelic strand is used in each repeat to identify the DNA molecule (see figure description for figure 3, the test was run with both DQA1*0102 and DQA1*0501 as the reference probe).

Zimmerman *et al.* use sequence specific oligonucleotide analysis to confirm the identity of the alleles tested (see Figure 3 legend). The method taught by Zimmerman *et al.* can distinguish the second exons of alleles 0102 and 0103, and these differ by only two nucleotides (see figures 1 and 2). In the methods taught by Zimmerman *et al.* the complementary reference strand and the DNA molecule have the same number of nucleotides, as these are both fragments amplified using the same primers (p. 4542). In the method taught by Zimmerman *et al.* the control duplexes are duplexes which have graded motilities and which are run in a different lane on the gel to the test duplex. Zimmerman *et al.* specifically teach that "every DQA1 allele, with the exception of DQA1*0601 can be distinguished by the unique mobility of one or both of its HD bands." Zimmerman *et al.* teach steps prior to step (a) which include amplifying a DNA molecule to produce double stranded DNA molecules and denaturing the amplified double

stranded DNA molecules into single use PCR prior to step (a) (see p. 4542, PCR amplification) and then denature the amplified double stranded DNA molecule into single stranded DNA molecules (see p. 4542, DHDA).

Zimmerman *et al.* demonstrate the use of their method for the determination of HLA DQA1 type for a family. In order to do so, they run the heteroduplexes out on an electrophoretic gel, assess the position of the bands, compare the test duplexes to a database of reference duplexes. The left side of the gel in Figure 3 is considered to be a database of test duplex migration values.

Zimmerman *et al.* do not assign an "exact migration value" to the distance traveled by the heteroduplexes, wherein such a value requires that some numerical value be assigned to the distance traveled. However, Zimmerman *et al.* very clearly demonstrate that each allele travels a distinct distance (i.e. see figures 2-4), and in fact state that the "identifying novel alleles is based on positive detection of HD products with unique electrophoretic mobilities (p. 4545)."

Mullins *et al.*, in example 4, provide methodology and examples of the assignment of exact numeric hierodule mobility migration values. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have assigned exact migration values to the movement of heteroduplexes in the methods taught by Zimmerman *et al.* The ordinary practitioner would have been motivated to do so by the teachings of Zimmerman *et al.* which clearly state that the identification of alleles is based on the distance traveled on the gel compared with the test duplexes. Thus the ordinary practitioner would have been motivated to use a measurement method such as the one taught by Mullins *et al.* in order to have provided a clear and quantitative methodology for allele identification. With regard to claim 76, the

assignment of migration values which are comparative to the control duplex is inherent in the method taught by Zimmerman *et al.* because the determination of the alleles present is a matter of comparison between the database of reference duplexes and the test duplexes. Thus, the determination of the allele present is a matter of comparing the distance traveled between the reference duplexes and the test duplexes.

Zimmerman *et al.* do not teach a method in which the identified DNA molecule is matched to a second identified DNA molecule and the method is used to match tissue between a prospective tissue donor and prospective tissue recipient. However, Zimmerman *et al.* do teach that identifying the molecular diversity within MHC class II molecules has been motivated in large part by the clinical significance of matching donor and host in solid organ and kidney transplants (p. 4541), and that their method provides many advantages over the state of the art SSO-typing methodologies, including a reduced number of probes needed and the ability to use lower stringency conditions, thus eliminating the need for tight control of hybridization and washing conditions, since identification is based on the detection of HD products with unique electrophoretic mobilities (p. 4545). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the method of genotyping taught by Zimmerman *et al.* for tissue donor matching since Zimmerman *et al.* teach the need for typing methods in donor-tissue situations, and Zimmerman *et al.* provide a method with the benefits as discussed.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1655

October 5, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600